

PUBLISHED AS A SUPPLEMENT TO
PSYCHOMETRIKA

EDITED BY N. RASHEVSKY
The University of Chicago · Chicago, Illinois

**VOLUME 1
NUMBER 3
SEPTEMBER
1939**

The Bulletin is published quarterly and is devoted to publications of research in Mathematical Biophysics, as contributing to the physico-mathematical foundations of biology.

All inquiries concerning publications should be addressed to the editor of the BULLETIN.

THE BULLETIN OF MATHEMATICAL BIOPHYSICS is sent free of charge during 1939 to all members of the Psychometric Society. Other individuals and libraries may secure a copy of all issues of the Bulletin during 1939 by payment of \$2.50. Checks should be made payable to the Psychometric Corporation and mailed to N. RASHEVSKY, The University of Chicago, Chicago, Ill.

BULLETIN OF
Mathematical Biophysics

CONTENTS

MATHEMATICAL BIOPHYSICS OF GROWTH - - - - 119
N. RASHEVSKY

STUDIES IN THE MATHEMATICAL THEORY OF EXCI-
TATION - - - - - 129
A. S. HOUSEHOLDER

DIFFUSION IN COLLOIDAL MEDIA - - - - - 143
JOHN M. REINER

VOLUME ONE SEPTEMBER 1939 NUMBER THREE

MATHEMATICAL BIOPHYSICS OF GROWTH

N. RASHEVSKY

The University of Chicago.

The rate of growth of a tissue is studied mathematically in its dependence on the metabolism of the cells. A high glycolytic coefficient, which facilitates cell division, as has been shown before, does in this way also increase indirectly the rate of growth of the tissue. There is however also a possible direct effect of glycolysis on the rate of growth, which is also studied analytically. Equations are derived, giving the total rate of growth of a tissue in its dependence on the glycolytic coefficient.

In our book (Rashevsky, 1938, hereinafter referred to as MB) we have derived some relations (MB, Chapt. X), showing that the forces which tend to divide a cell are the stronger the greater the glycolytic coefficient β of the cell, and pointed out, that this is in a certain agreement with Warburg's findings, that abnormally rapidly multiplying cancer cells exhibit an abnormally high glycolytic coefficient. An abnormally easy cell division is however not directly connected with an abnormal rate of growth of the cellular aggregate as a whole, and it is the abnormal rate of growth that is especially characteristic of tumors. In the present paper we shall give some general theoretical discussions of possible relations between glycolysis and rate of growth.

I.

Following the method developed in the *Appendix* of MB., we shall consider cells of an arbitrary shape. When they are not too elongated, they are characterized by their average overall size a .

Let a substance enter such a cell and be consumed there at a rate Q proportional to the concentration \bar{c} ,

$$Q = k\bar{c} . \quad (1)$$

Denoting by c_0 the external concentration, by \bar{c} the average internal concentration, by c_1 the internal concentration at the membrane, and using the same argument as before, we have (Rashevsky, 1939):

$$4\pi ha^2(c_0 - c_1) = \frac{4}{3} \pi a^3 k \bar{c} \quad (2)$$

and

$$4\pi ha^2(c_0 - c_1) = 8\pi a^2 D \frac{c_1 - \bar{c}}{a}; \quad (3)$$

or

$$h(c_0 - c_1) = \frac{ak\bar{c}}{3} \quad (4)$$

and

$$h(c_0 - c_1) = 2D \frac{c_1 - \bar{c}}{a}. \quad (5)$$

Combining (4) and (5) and rearranging:

$$c_1 = (1 + \frac{a^2 k}{6D}) \bar{c}. \quad (6)$$

Substituting (6) into (4) we find:

$$\bar{c} = \frac{c_0}{1 + \frac{a^2 k}{6D} + \frac{ak}{3h}}. \quad (7)$$

If the molecules of the substance are rather large (amino-acids), so that D and h have small values, of the order of $D \sim 10^{-10} \text{ cm}^2 \cdot \text{sec}^{-1}$; $h \sim 10^{-6} \text{ cm} \cdot \text{sec}^{-1}$, we find for $a \sim 10^{-3} \text{ cm}$, $k \sim 10^{-2} \text{ sec}^{-1}$; $c_0 \sim 10^{-4} \text{ gr} \cdot \text{cm}^{-3}$

$$\frac{a^2 k}{6D} \sim \frac{ak}{3h} \sim 10 > 1. \quad (8)$$

For simplicity consider the special case, in which $D \sim 10^{-10} \text{ cm}^2 \text{sec}^{-1}$ but $h \gg 10^{-6} \text{ cm} \cdot \text{sec}$. Then equ. (7) reduces to:

$$\bar{c} = \frac{6Dc_0}{a^2 k}. \quad (9)$$

Let the substance be transformed into another one, forming the body of the cell (proteins). Let the latter break down at a constant rate $q \text{ gr} \cdot \text{cm}^{-3} \cdot \text{sec}^{-1}$. Denoting by V the volume of the cell, we then have for a constant concentration δ of that other substance:

$$\delta \frac{dV}{dt} = k\bar{c}V - qV. \quad (10)$$

Introducing (9) into (10) and remembering that $V = \frac{4}{3}\pi a^3$, we find:

$$\delta \frac{da}{dt} = \frac{2Dc_0}{a} - \frac{aq}{3}. \quad (11)$$

The size a tends to a limiting value \bar{a} , obtained by making the right hand side of (11) equal to zero. This gives:

$$\bar{a} = \sqrt{\frac{6Dc_0}{q}}. \quad (12)$$

Taking for $q \approx 10^{-9}$ gr.cm⁻³.sec⁻¹, a value found for the breakdown of cell proteins (MB, p. 104) we find:

$$\bar{a} \approx 10^{-2} \text{ cm}. \quad (13)$$

In actual cases not one, but several substances (amino-acids) are consumed, building up cell proteins. Let there be n substances consumed each at a rate $k_i \bar{c}_1 \bar{c}_2 \dots \bar{c}_n$. For the i -th substance the rate of consumption may be written:

$$k_i (\bar{c}_1 \bar{c}_2 \dots \bar{c}_{i-1} \bar{c}_{i+1} \dots \bar{c}_n) \bar{c}_i. \quad (14)$$

The expression $k_i (c_1 c_2 \dots c_{i-1} c_{i+1} \dots c_n)$ plays the role of k in equ. (1). By a similar argument as before we find approximately

$$\bar{c}_i = \frac{6D_i c_{0i}}{a^2 k_i \bar{c}_1 \bar{c}_2 \dots \bar{c}_{i-1} \bar{c}_{i+1} \dots \bar{c}_n} \quad (15)$$

where c_{0i} is the external concentration of the i -th substance. Hence:

$$\bar{c}_1 \bar{c}_2 \dots \bar{c}_n = \frac{6^n D_1 D_2 \dots D_n c_{01} c_{02} \dots c_{0n}}{a^{2n} k_1 k_2 \dots k_n (\bar{c}_1 \bar{c}_2 \dots \bar{c}_n)^{n-1}}; \quad (16)$$

or

$$\bar{c}_1 \dots \bar{c}_n = \frac{6 \sqrt[n]{D_1 \dots D_n} \sqrt[n]{c_{01} \dots c_{0n}}}{a^2 \sqrt[n]{k_1 \dots k_n}} = \frac{6 \bar{D} \bar{c}_0}{a^2 \bar{k}}; \quad (17)$$

which is of the same form as (9). For brevity we shall write here D, k etc. as if one substance only were present.

From the discussion in Chapt. X of MB, which leads to the inequality (8) on p. 105, it follows that the resulting "equivalent" outflow is of the form

$$\bar{q} = A\beta - B, \quad (18)$$

where β is the glycolytic coefficient and A and B are functions of temperature, diffusion coefficients and molecular weights.

The critical stability size a^* is given (MB, Appendix) by

$$a^* = \sqrt[3]{\frac{9MD_1\gamma}{RTq_\mu}} = \sqrt[3]{\frac{9\bar{M}\bar{D}_1\gamma}{RT(A\beta - B)_\mu}}, \quad (19)$$

where \bar{M} and \bar{D}_1 are some sort of averages of the values for the different metabolites involved in the *respiratory* metabolism. The values of \bar{D}_1 is different from that of D , the latter referring to amino-acids.

If $a^* > \bar{a}$, as given by (12) then the cell does not divide at all.

If $a^* < \bar{a}$, then a cell divides as soon as $a = a^*$.

Equ. (11) gives:

$$\frac{\delta}{2} \frac{da^2}{2Dc_0 - \frac{q}{3}a^2} = dt ;$$

which after elementary integration and rearrangement gives:

$$a^2 = \frac{6Dc_0}{q} - C e^{-\frac{2q}{3\delta}t} \quad (20)$$

where C is an integration constant.

If the cell divides at $a = a^*$, then each half cell has the size $a' = 0,795 a^*$, or

$$a'^2 = 0,63 a^{*2} \quad (21)$$

At this size it starts growing again. We take the moment at which $a = a'$ as $t = 0$. Hence for $t = 0$

$$\frac{6Dc_0}{q} - C = 0,63 a^{*2} ,$$

or

$$C = \frac{6Dc_0}{q} - 0,63 a^{*2} \quad (22)$$

Hence, introducing (22) into (20):

$$a^2 = \frac{6Dc_0}{q} - \left(\frac{6Dc_0}{q} - 0,63 a^{*2} \right) e^{-\frac{2q}{3\delta}t} \quad (23)$$

The value Δt of the time interval between two successive divisions is found by equating the right hand side of (23) to a^{*2} (since for $t = 0$, $a = a'$), and putting $t = \Delta t$. This gives after some rearrangements:

$$e^{-\frac{2q}{3\delta}\Delta t} = \frac{6Dc_0 - qa^{*2}}{6Dc_0 - 0,63qa^{*2}} ,$$

or

$$\Delta t = \frac{3\delta}{2q} \log \frac{6Dc_0 - 0,63qa^{*2}}{6Dc_0 - qa^{*2}} \quad (24)$$

If in an aggregate of N cells every cell divides every Δt seconds, then from N cells every Δt seconds N new cells are made. Hence

$$\frac{dN}{dt} = \frac{N}{\Delta t},$$

or

$$N = N_0 e^{\frac{t}{\Delta t}}. \quad (25)$$

Introducing (19) into (24) and the latter into (25), we obtain the rate of growth of a cellular aggregate as a function of the glycolytic coefficient β . The larger β , the smaller a^* , the smaller Δt and the more rapid the growth. The increase of a with time between divisions is practically linear for large β 's; convex upwards for small β 's.

Equ. (24) may be written:

$$\Delta t = \frac{3\delta}{3q} \log \frac{1 - \frac{0.63 qa^{*2}}{6Dc_0}}{1 - \frac{qa^{*2}}{6Dc_0}}. \quad (26)$$

With values used above, $qa^{*2}/6Dc_0 \sim 10^{-2} \ll 1$. Hence (26) may be written:

$$\Delta t = \frac{0.09 \delta}{Dc_0} a^{*2}. \quad (27)$$

Taking $\delta \sim 10^{-1}$, as representing the order of magnitude of the dry weight of a cell, we find with the values used here for the different constants, $\Delta t \sim 1 - 10$ days.

Introducing (19) into (27) and the latter into (25) we find:

$$N = N_0 e^{\frac{Dc_0}{0.09 \delta} \left(\frac{RT(A\beta - B)}{M\bar{D}_1\gamma} \right)^{2/3} t}. \quad (28)$$

In this simple theory, a tissue grows the faster, the greater β , other conditions being equal. But a faster growing tissue should have also smaller cells, other conditions being equal. It may be remarked that cells of an early embryo are usually smaller than cells of an adult organism.

II

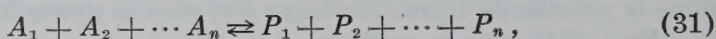
Glycolysis may however influence the rate of growth in a more direct way, than that considered above. When β is large, the net effective metabolic flow is directed outwards and results in a pressure on the cell membrane directed outward. For an approximately constant \bar{q} , this pressure is equal (MB, Chapt. VIII) to

$$\frac{RT}{M} \frac{\bar{q}a}{3\bar{h}}, \quad (29)$$

where \bar{h} again refers to an average value for respiratory metabolites. The pressure (29) may be partially compensated by a static osmotic pressure p_0 , due to different nonmetabolised substances, dissolved in the cell and in the surrounding, for which the membrane may be impermeable. The total pressure then is equal to

$$\frac{RT}{M} \frac{\bar{q}a}{3\bar{h}} - p_0. \quad (30)$$

Let a reversible reaction take place in the cell:



where A_i represents some aminoacid, and P_i a protein. If this reaction requires a special enzyme, which is present only inside of the cell, then it will not take place outside of the cell. If the membrane is permeable to A_i but not to P_i , then the concentrations of A_i will be the same inside of the cell and outside, and if the cell size remains constant, the amounts of P_i will not change, everything remaining static. Let however, due to some cause, the cell size increase *very slowly*. Then the concentrations of A_i and P_i will decrease. But due to the supply from outside, the concentration of A_i will be practically immediately reestablished. Thus the concentration of A_i will remain the same, that of P_i decrease. As a result of this some P_i will be formed according to (31). The cause of the increase may be the pressure (30), which tends to expand the cell. According to this picture a cell does not grow in size because of increase in mass, but rather increases in mass because of growth in size.

In the first approximation the increase of size a will be proportional to (30) and given by

$$\frac{da}{dt} = \zeta \left(\frac{RT}{M} \frac{\bar{q}a}{3\bar{h}} - p_0 \right), \quad (32)$$

where ζ is principally determined by the resistance of the membrane to the flow of water, which due to its incompressibility must flow into the cell as soon as the latter expands. Equ. (32) integrated gives:

$$a = \frac{3\bar{M}\bar{h}p_0}{RT\bar{q}} + C e^{\frac{RT\bar{q}}{3\bar{M}\bar{h}}t}. \quad (33)$$

C being an integration constant.

For β just above the critical value $\beta_0 = B/A$, when $\bar{q} = A\beta - B$ is positive but very small, such a cell might grow to tremendous dimensions, though the rate of growth would be extremely slow. For normal β it will grow to a normal size a^* and then divide. Again, as before, let us put $t = 0$, when $a = 0, 8a^*$. Hence

$$\frac{3\bar{M}\bar{h}p_0}{RT\bar{q}} + C = 0, 8a^*, \quad (34)$$

or

$$C = 0, 8a^* - \frac{3\bar{M}\bar{h}p_0}{RT\bar{q}}. \quad (35)$$

Therefore

$$a = \frac{3\bar{M}\bar{h}p_0}{RT\bar{q}} + (0, 8a^* - \frac{3\bar{M}\bar{h}p_0}{RT\bar{q}}) e^{\frac{RT\bar{q}}{3\bar{M}\bar{h}}t}. \quad (36)$$

The interval Δt between two successive divisions is given by

$$\frac{3\bar{M}\bar{h}p_0}{RT\bar{q}} + (0, 8a^* - \frac{3\bar{M}\bar{h}p_0}{RT\bar{q}}) e^{\frac{RT\bar{q}}{3\bar{M}\bar{h}}\Delta t} = a^*,$$

or solving for Δt

$$\Delta t = \frac{3\bar{M}\bar{h}}{RT\bar{q}} \log \frac{RT\bar{q}a^* - 3\bar{M}\bar{h}p_0}{0, 8RT\bar{q}a^* - 3\bar{M}\bar{h}p_0}. \quad (37)$$

For very small values of p_0 , (37) reduces to

$$\Delta t = \frac{3\bar{M}\bar{h}}{RT\bar{q}} \log 1, 25 = \frac{0, 67\bar{M}\bar{h}}{RT\bar{q}}, \quad (38)$$

which introduced into (25), gives:

$$N = N_0 e^{\frac{RT\bar{q}}{0, 67\bar{M}\bar{h}}t}. \quad (39)$$

As p_0 increases and approaches the value $0, 8RT\bar{q}a^*/3\bar{M}\bar{h}$, Δt approaches infinity, because for large values of p_0 the net pressure (30) is directed inward and the cell does not grow.

The larger β , the larger \bar{q} and the larger the rate of growth. The cell size a^* does not need however to be smaller in this case, in spite of a larger \bar{q} , since (39) does not contain \bar{D}_1 . If \bar{D}_1 increases in the same ratio as \bar{q}/\bar{M} , a^* remains unchanged. This holds *a fortiori* if instead of (38) we use the more exact expression (37).

An increase of ζ in (39) results in an increased rate of growth. On general physical grounds we would expect \bar{h} and ζ to increase simultaneously, though not necessarily in the same ratio. Nothing can be said therefore about the influence of \bar{h} on the rate of growth, until we possess a better developed theory of permeability. From what was said above about the role of \bar{D}_1 , it follows that more rapidly growing cells should have a larger \bar{D}_1 , if their size is not smaller than that of slower growing cells. Inasmuch as cancer cells are found of any size within normal range, we may expect them to possess a higher \bar{D}_1 which would agree with the observations concerning their higher water content and higher general permeability.

III

We may also consider other limiting factors for the cell size than the mechanical instability or the one given by equ. (12). Let the respiratory reaction be catalized by some enzyme, whose concentration is $m \text{ gr} \cdot \text{cm}^{-3}$, so that

$$\bar{q} = \alpha m, \quad (40)$$

α being a coefficient of proportionality. Let m vary according to the equation:

$$\frac{dm}{dt} = k' \bar{c} - q', \quad (41)$$

where q' is a constant and \bar{c} is the concentration of a substance, which flows into the cell, and is there transformed at a rate $k'\bar{c}$ forming the catalist. In this case \bar{c} is given by (9). Hence

$$\frac{dm}{dt} = \frac{6D'c'_0}{a^2} - q'. \quad (42)$$

D' and c'_0 in (42) are of course different from D and c_0 in (9). Equ. (42) will hold with good approximation even when the size of the cell is not constant, but increases with time very slowly, so that the quasi-stationary diffusion equation may be applied (MB, Chapt. I). For

$$\frac{6D'c'_0}{a^2} < q',$$

or

$$a > \sqrt{\frac{6D'c'_0}{q'}} = a_m, \quad (43)$$

dm/dt becomes negative. Hence m and therefore also $\bar{q} = \alpha m$ will decrease, when the cell exceeds the size a_m . For sufficiently large a , \bar{q} will rapidly become so small, that $RT\bar{q}a/3M\bar{h} = p_0$, and therefore $da/dt = 0$, because of (32).

Or m may vary like

$$\frac{dm}{dt} = k'\bar{c}' - k''m. \quad (44)$$

Again if a does not vary too rapidly, we have for each a the quasi-stationary value:

$$m = \frac{6D'c'_0}{k'a^2}. \quad (45)$$

Hence from (45) and (40)

$$\bar{q} = \frac{6\alpha D'c'_0}{k'a^2}. \quad (46)$$

Because of (32), the cell will not grow above the size, given by

$$\frac{RT\bar{q}a}{3M\bar{h}} = p_0. \quad (47)$$

Introducing (46) into (47) we find for the limiting size

$$a = \frac{2RT\alpha D'c'_0}{Mk'\bar{h}p_0}. \quad (48)$$

The author is indebted to Mr. H. D. Landahl for the checking of calculations and for several critical remarks.

REFERENCES

- Rashevsky, N. 1938. *Mathematical Biophysics. Physicomathematical Foundations of Biology*. Chicago; The University of Chicago Press.
 Rashevsky, N. 1939. "The Mechanism of Cell Division". *Bull. Math Biophysics*. 1, 1939.

STUDIES IN THE MATHEMATICAL THEORY OF EXCITATION

A. S. HOUSEHOLDER

The University of Chicago

The general linear two-factor nerve-excitation theory of the type of Rashevsky and Hill is discussed and normal forms are derived. It is shown that in some cases these equations are not reducible to the Rashevsky form. Most notable is the case in which the solutions are damped periodic functions. It is shown that in this case one or more—in some cases infinitely many—discharges are predictable, following the application of a constant stimulus S . The number of discharges increases with S , but the frequency is a constant, characteristic of the fiber and independent of S .

1. *The general linear two-factor theory.* The two-factor nerve-excitation theories of Rashevsky (1933) and of Hill (1936) are natural generalizations of the single-factor theory of Blair (1932), which supply several of the deficiencies of Blair's theory. At the same time these have not appeared to yield repetitive discharges of the nerve fiber under constant stimulation, a phenomenon which is often met with empirically. It is the purpose of the present discussion to consider the most general possible linear two-factor theory, and to show in particular that for suitable choices of the parameters of the equations such repetitive discharges are predictable.

In its most general terms the two-factor theory postulates the capacity of the nerve fiber to develop two "substances" or "factors", the rate of development of each being a linear homogeneous function of the three quantities: the stimulus intensity, and the excess of each substance or factor over the resting value. Excitation is supposed to occur and to continue as long as a certain linear homogeneous function of the measures of these factors is positive.

We shall speak of the factors as substances, for convenience and definiteness of the picture, though they do not need to be such, and we shall speak of their concentrations as measures of the factors. Then if x_1 and x_2 are the concentrations at any time t , and if $S(t)$ is the stimulus intensity, then the development of the substances is governed by the linear differential equations

$$\begin{aligned}\frac{dx_1}{dt} &= a_{11}(x_1 - x_1^0) + a_{12}(x_2 - x_2^0) + \alpha_1 S(t), \\ \frac{dx_2}{dt} &= a_{21}(x_1 - x_1^0) + a_{22}(x_2 - x_2^0) + \alpha_2 S(t),\end{aligned}\tag{1}$$

where x_1^0 and x_2^0 are the concentrations in the resting fiber. Since we are by no means insisting that they really are substances being developed, we shall not require that x_1 and x_2 be positive to be meaningful.

By suitable choice of units and of subscripts, it is no restriction to assume that the condition for excitation be of the form

$$x_1 - x_2 > 0, \tag{2}$$

the left member of the inequality being the linear homogeneous function referred to above.

Empirically only $S(t)$ and the resulting interval of excitation are measurable, that is to say, only $S(t)$ and the times at which the inequality (2) is satisfied. Hence we shall *define two forms of the two-factor theory as being equivalent in case the corresponding inequalities (2) are simultaneously satisfied*. With this definition of equivalence we shall investigate the conditions for equivalence of any two two-factor theories and deduce normal forms for these.

Blair's theory is obtainable by setting $a_{12} = a_{21} = a_{22} = \alpha_2 = 0$ in (1). Rashevsky's theory assumed $a_{12} = a_{21} = 0$, while Hill's theory had $a_{12} = \alpha_2 = 0$. Offner (1937), seeking to test Rashevsky's and Hill's theory experimentally, found that they were, in fact, equivalent in the sense defined above. Young (1937) then showed that the most general two-factor theory (1) could in general be formally reduced to the Rashevsky form. However, when the characteristic roots are complex so are the resulting coefficients in the Rashevsky form. Physically this is the case of (damped) periodicity with possible repetitive discharge, and is most conveniently studied by reducing to a non-Rashevsky form with real coefficients. Rashevsky (1938) has reviewed completely the case of the equations in his form with real characteristic roots, summarizing the equivalence proofs of Offner and of Young, and discussing empirical checks.

2. *Roots real and distinct.* Equations (1) can be written in matrix notation in the form

$$\frac{dx}{dt} = a(x - x^0) + \alpha S(t), \tag{3}$$

where S is a scalar, α , x and x^0 are column vectors, and a is a two-by-two matrix. Any linear substitution

$$y = c x, \quad \frac{dy}{dt} = c \frac{dx}{dt}, \quad (4)$$

where the matrix c is a non-singular matrix of constants, transforms the linear differential equations (3) into the linear differential equations

$$\frac{dy}{dt} = b(y - y^0) + \beta S(t) \quad (5)$$

where

$$b = c a c^{-1}, \quad \beta = c \alpha. \quad (6)$$

However, we can admit only those matrices c for which inequality (2) and the inequality

$$y_1 - y_2 > 0 \quad (7)$$

are simultaneously satisfied. Such matrices c will be said to define an *admissible substitution*. Any equations (3) and (5) obtainable one from the other by an admissible substitution are equivalent in our sense.

It is at once evident that a scalar matrix

$$c = \begin{pmatrix} \rho & 0 \\ 0 & \rho \end{pmatrix}, \quad \rho > 0 \quad (8)$$

defines an admissible substitution. This has the effect only of multiplying the two coefficients α_1 and α_2 by the same positive scalar factor ρ . Hence, *only the ratio* $\alpha_1 : \alpha_2$ *is important*, and we may, for example, at any time assume α_1 and α_2 to be the sine and the cosine of some angle.

We next recall the well known theorem in algebra which states that for *any* non-singular matrix c , the characteristic roots of the matrices a and $c a c^{-1}$ are the same. These are the roots λ_1 and λ_2 of the quadratic equation

$$|a - \lambda I| = 0, \quad (9)$$

where I is the identity matrix. Hence if an admissible substitution exists such that the matrix b is diagonal, b has necessarily the form

$$\begin{pmatrix} \lambda_1 & 0 \\ 0 & \lambda_2 \end{pmatrix}. \quad (10)$$

We can easily write down the matrix c defining such an admissible substitution, when the roots λ_1 and λ_2 are real and distinct, by referring to some principles of projective geometry. Consider the transformation

$$\xi' = a \xi \quad (11)$$

of the elements (ξ_1, ξ_2) of a one-dimensional projective form into the elements (ξ'_1, ξ'_2) of this same form. When the roots λ_1 and λ_2 are real and distinct there are two real and distinct fixed elements, i.e. two elements of the one-dimensional form, (ξ_1^1, ξ_2^1) and (ξ_1^2, ξ_2^2) which are transformed into themselves by the transformation (11). These are given by the two pairs of dependent homogeneous equations

$$\lambda_i \xi^i = a \xi^i, \quad (i = 1, 2), \quad (12)$$

If we introduce new coordinates into this projective form by the coordinate substitution

$$\eta = c \xi, \quad \eta' = c \xi', \quad (13)$$

then the transformation (11) is equivalent to

$$\eta' = c a c^{-1} \eta. \quad (14)$$

Now a projective coordinate system in a one-dimensional form is fixed when the projective coordinates of three elements of the form are assigned. Let us, therefore, assign to the point ξ^1 the η -coordinates $(1,0)$, to ξ^2 the η -coordinates $(0,1)$ and to $(1,1)$ the η -coordinates $(1,1)$. Evidently, then, the points $(1,0)$ and $(0,1)$ are the fixed points of the transformation (14), and therefore this takes the form

$$\eta'_i = \lambda_i \eta_i. \quad (15)$$

Since the required coordinate substitution changes the coordinates of ξ^1 and ξ^2 into $(1,0)$ and $(0,1)$ respectively, and leaves the coordinates of $(1,1)$ unchanged, it is easy to write down this substitution explicitly in terms of the ξ_i^j by expressing the fact that the anharmonic ratio of an arbitrary ξ with ξ^1, ξ^2 and $(1,1)$ is equal to the anharmonic ratio of the corresponding η with $(1,0), (0,1)$ and $(1,1)$. If we write, then, x and y in place of ξ and η for the variable point we obtain the desired form of the substitution (4):

$$y_1 = \rho \frac{\xi_2^2 x_1 - \xi_1^2 x_2}{\xi_2^2 - \xi_1^2}, \quad y_2 = \rho \frac{\xi_2^1 x_1 - \xi_1^1 x_2}{\xi_2^1 - \xi_1^1}, \quad (16)$$

where ρ is an arbitrary constant.

One thing remains to be determined. We observe that interchanging the notations ξ^1 and ξ^2 of the two fixed points, or, what comes to the same thing, interchanging the subscripts on the two characteristic roots λ_1 and λ_2 , has the effect of interchanging y_1 and y_2 . Whichever root is called λ_1 and whatever the sign of ρ , the equations $x_1 = x_2$ and $y_1 = y_2$ will be simultaneously satisfied, but unless these are properly

associated the orders of the *inequalities* will be reversed. For definiteness we require that

$$\rho > 0. \quad (17)$$

It is no restriction if we so choose the homogeneous coordinates of ξ^1 and ξ^2 that

$$\xi_2^1 - \xi_1^1 = 1. \quad (18)$$

Then we have

$$y_2 - y_1 = \rho \{ (\xi_2^1 - \xi_2^2) x_1 - (\xi_1^1 - \xi_1^2) x_2 \}.$$

But by subtracting equations (18) one from the other we find that

$$\xi_2^1 - \xi_2^2 = \xi_1^1 - \xi_1^2,$$

whence

$$y_1 - y_2 = \rho (\xi_2^2 - \xi_2^1) (x_1 - x_2). \quad (19)$$

Thus *in order that the inequalities (2) and (7) shall be simultaneously satisfied the designations λ_1 and λ_2 must be assigned to the characteristic roots in such a way that*

$$\xi_2^2 - \xi_2^1 > 0 \quad (20)$$

when the scalar factor ρ is chosen positive and the homogeneous coordinates of the fixed points are chosen to satisfy (18).

From equation (6) we have

$$\beta_1 = \rho (\xi_2^2 \alpha_1 - \xi_1^2 \alpha_2), \quad (21)$$

$$\beta_2 = \rho (\xi_2^1 \alpha_1 - \xi_1^1 \alpha_2).$$

Varying the scalar factor ρ does not affect the matrix b , but only the magnitudes of the coefficients β . Hence, we may choose this scalar factor so that

$$\beta_1^2 + \beta_2^2 = 1 \quad (22)$$

and hence so that β_1 and β_2 are the cosine and the sine of some angle. This is in accordance with the statement made above that only the ratio of the coefficients of $S(t)$ is important. Note that

$$\beta_1 - \beta_2 = \rho (\xi_2^2 - \xi_2^1) (\alpha_1 - \alpha_2), \quad (23)$$

so that *the quantities $\beta_1 - \beta_2$ and $\alpha_1 - \alpha_2$ have the same sign*. Nothing can be said, however, about the signs of β_1 and β_2 separately.

We have tacitly assumed, in the foregoing discussion, that the point (1,1) is not itself a double-point of the transformation (11). Postponing, for the moment, our consideration of this possibility, we may summarize:

Let the excitation equations in the explicit form (1) or the matrix form (3) be such that the roots λ_1 and λ_2 of the quadratic equation (9) are real and distinct. Let the vectors ξ^1 and ξ^2 , which satisfy the matrix equations (12), both have unequal components. Then their components can be chosen to satisfy (18) and the indices can be so adjusted that (20) is satisfied. Then the substitution (16) with an arbitrary positive scalar ρ is admissible and transforms the equations (1) into the equations

$$\begin{aligned}\frac{dy_1}{dt} &= \lambda_1(y_1 - y_1^0) + \beta_1 S(t), \\ \frac{dy_2}{dt} &= \lambda_2(y_2 - y_2^0) + \beta_2 S(t),\end{aligned}\tag{24'}$$

where β_1 and β_2 are given by (21). The scalar ρ can further be specified so that (22) is satisfied, and in this case the equations (24') can be written

$$\begin{aligned}\frac{dy_1}{dt} &= \lambda_1(y_1 - y_1^0) + S(t) \cos \beta, \\ \frac{dy_2}{dt} &= \lambda_2(y_2 - y_2^0) + S(t) \sin \beta,\end{aligned}\tag{24}$$

for some angle β . This is the Rashevsky form of the excitation equations, and it contains five essential parameters. For stability to exist, and non-excitation in the resting state, it is necessary that

$$\lambda_1 < 0, \quad \lambda_2 < 0, \quad y_1^0 < y_2^0,\tag{25}$$

while from the nature of the substitution it follows that $\beta_1 - \beta_2$ and $\alpha_1 - \alpha_2$ satisfy (23) and hence have the same sign.

In the exceptional case when (1,1) is a fixed point of the transformation (11) there is no substitution (4) admissible in our sense which throws the excitation equations into the Rashevsky form. If λ_1 is the root corresponding to the fixed point (1,1) and if λ_2 is the other root, the equations (1) are in the form

$$\begin{aligned}\frac{dx_1}{dt} &= a(x_1 - x_1^0) + (\lambda_1 - a)(x_2 - x_2^0) + \alpha_1 S(t), \\ \frac{dx_2}{dt} &= (a - \lambda_2)(x_1 - x_1^0) + (\lambda_1 + \lambda_2 - a)(x_2 - x_2^0) + \alpha_2 S(t),\end{aligned}\tag{26}$$

where a is some constant. The other fixed point is then $(a - \lambda_1, a - \lambda_2)$. We may make a substitution which gives to this point the

coordinates $(0,1)$, in which case the excitation equations take the form

$$\begin{aligned}\frac{dy_1}{dt} &= \lambda_1(y_1 - y_1^0) + \beta_1 S(t), \\ \frac{dy_2}{dt} &= (\lambda_1 - \lambda_2)(y_1 - y_1^0) + \lambda_2(y_2 - y_2^0) + \beta_2 S(t),\end{aligned}\tag{27}$$

where the coefficients β are yet to be determined and we may still assign the projective coordinates of another point. But β_1 and β_2 are the projective η -coordinates of the point whose coordinates are (α_1, α_2) in the ξ -system. Hence the following statement is immediately evident:

In the exceptional case when $(1,1)$ is a fixed point of the transformation (11), the excitation equations cannot be given the Rash-evsky form by any admissible substitution, but they can be given the form (27). In these equations λ_1 is the root of (9) corresponding to the fixed point $(1,1)$, and λ_2 is the other root. To obtain this form one has only to choose a substitution keeping fixed the coordinates of $(1,1)$ and giving to the other fixed point the coordinates $(0,1)$. As for the coefficients β , there are three possibilities:

a. *if $\alpha_1 = \alpha_2$, then $\beta_1 = \beta_2$ whatever substitution of this type one employs;*

b. *if (α_1, α_2) is the second fixed point of the transformation (11) then $\beta_1 = 0$ and β_2 is -1 or $+1$ according as $\alpha_1 - \alpha_2$ is positive or negative;*

c. *if the coefficients α do not satisfy either relation, then β_1 and β_2 can be given arbitrary distinct values, $\beta_1 \neq \beta_2$, and in particular β_2 can be made equal to zero and β_1 equal to $+1$ or -1 according as $\alpha_1 - \alpha_2$ is positive or negative.*

In case *c* the substitution is uniquely determined since the coordinates of the three points whose initial coordinates are $(1,1)$ ($\alpha - \lambda_1$, $\alpha - \lambda_2$) and (α_1, α_2) are assigned. In cases *a* and *b* the point (α_1, α_2) coincides projectively with one of the other two, and the third point may be chosen at will.

3. *Roots real and equal.* If the characteristic roots are equal, $\lambda_1 = \lambda_2 = \lambda$, and the matrix b can be diagonalized, then it is a scalar matrix

$$c a c^{-1} = b = \begin{pmatrix} \lambda & 0 \\ 0 & \lambda \end{pmatrix},$$

whence

$$a = c^{-1} b c = b$$

since a scalar matrix is commutative with any matrix. Hence in the case of equal roots the excitation equations cannot be given the Rashevsky form unless they are initially in this form, and any (admissible) substitution leaves them in this form. If, in addition, $\alpha_1 = \alpha_2$, then the two quantities $x_1 - x_1^0$ and $x_2 - x_2^0$ satisfy the same differential equation, a case which is obviously of no importance. In the light of the discussion of the preceding section it is therefore evident that:

If the characteristic roots are equal, then the excitation equations cannot take the Rashevsky form unless they are initially of this form. In this case, however, it is physically necessary that $\alpha_1 \neq \alpha_2$, and the equations can be given the form

$$\begin{aligned}\frac{dy_1}{dt} &= \lambda (y_1 - y_1^0) \pm S(t), \\ \frac{dy_2}{dt} &= \lambda (y_2 - y_2^0),\end{aligned}\tag{28}$$

where the sign before $S(t)$ in the first equation is that of the quantity $\alpha_1 - \alpha_2$.

In the contrary case, when the excitation equations have equal characteristic roots but are not in the Rashevsky form, there is only one fixed element of the transformation (11). This can be given, say, the projective coordinates $(0,1)$ by an admissible substitution, provided it is not the element $(1,1)$. The original equations in this case can be written

$$\begin{aligned}\frac{dx_1}{dt} &= (\lambda + a) (x_1 - x_1^0) - \mu a (x_2 - x_2^0) + \alpha_1 S(t), \\ \frac{dx_2}{dt} &= \frac{a}{\mu} (x_1 - x_1^0) + (\lambda - a) (x_2 - x_2^0) + \alpha_2 S(t),\end{aligned}\tag{29}$$

where λ is the characteristic root and $(\mu, 1)$ is the fixed element. If $\alpha_1 \neq \alpha_2$ the substitution

$$y_1 = \rho \frac{x_1 - \mu x_2}{1 - \mu}, \quad y_2 = \rho \frac{\alpha_2 x_1 - \alpha_1 x_2}{\alpha_2 - \alpha_1},\tag{30}$$

where

$$\rho (\alpha_2 \mu - \alpha_1) (1 - \mu) (\alpha_2 - \alpha_1) > 0,\tag{31}$$

yields the form

$$\frac{dy_1}{dt} = \lambda(y_1 - y_1^0) \pm S(t), \quad (32)$$

$$\frac{dy_2}{dt} = b(y_1 - y_1^0) + \lambda(y_2 - y_2^0),$$

where

$$b = \frac{(\mu - 1)(\alpha_1 - \alpha_2 \mu)a}{\alpha_2 - \alpha_1}. \quad (33)$$

In case $\alpha_1 = \alpha_2$ we obtain the form

$$\frac{dy_1}{dt} = \lambda(y_1 - y_1^0) \pm S(t), \quad (34)$$

$$\frac{dy_2}{dt} = b(y_1 - y_1^0) + \lambda(y_2 - y_2^0) \pm S(t),$$

with a different expression for b . If $\mu = 1$ in (29), the fixed element is $(1, 1)$ and the substitution yielding the form (32) or (34) is no longer admissible.

If the characteristic roots $\lambda_1 = \lambda_2 = \lambda$ are equal, and the excitation equations are not in the Rashevsky form, they can be written in the form (29), where $(\mu, 1)$ is the single fixed element. If $\mu \neq 1$ and $\alpha_1 \neq \alpha_2$, a substitution of the form (30) yields the equations (32). If $\alpha_1 = \alpha_2$, it is possible to obtain the form (34). But if $\mu = 1$, neither of these forms is obtainable by an admissible substitution and one can only alter the form (29) by making the coefficients α_1 and α_2 equal to zero or unity.

4. *The characteristic roots complex.* In this case the roots are necessarily distinct, being conjugate complex. Let these be $\lambda \pm i\mu$. Then we choose the substitution which gives the coordinates $(1, -i)$ to the fixed point corresponding to the root $\lambda + i\mu$, and the coordinates $(1, i)$ to the fixed point corresponding to the root $\lambda - i\mu$. The excitation equations then take the form

$$\frac{dy_1}{dt} = \lambda(y_1 - y_1^0) - \mu(y_2 - y_2^0) + \beta_1 S(t), \quad (35)$$

$$\frac{dy_2}{dt} = \mu(y_1 - y_1^0) + \lambda(y_2 - y_2^0) + \beta_2 S(t).$$

The explicit form of the equations of substitution can be derived as explained previously, but they are slightly more complicated and we do not write them here. The substitution is uniquely determined up

to a scale factor ρ . It is convenient for the further discussion to adjust the time units so that

$$\lambda^2 + \mu^2 = 1. \quad (36)$$

This can always be done by substituting

$$\tau = t \sqrt{\lambda^2 + \mu^2} \quad (37)$$

and writing the corresponding equations in τ instead of t . Suppose this has been done, and let us then rename the variables, calling the time variable in the new units t instead of τ and the new coefficients and functions again λ , μ , β , and $S(t)$. Equation (36) is then satisfied and by a further choice of the scale factor ρ we can suppose that

$$\beta_1^2 + \beta_2^2 = 1. \quad (38)$$

Hence we may set

$$\lambda = \cos \gamma, \quad \mu = \sin \gamma, \quad (39)$$

$$\beta_1 = \cos \beta, \quad \beta_2 = \sin \beta,$$

and write our equations (35) in the form

$$\frac{dy_1}{dt} = (y_1 - y_1^0) \cos \gamma - (y_2 - y_2^0) \sin \gamma + S(t) \cos \beta, \quad (40)$$

$$\frac{dy_2}{dt} = (y_1 - y_1^0) \sin \gamma + (y_2 - y_2^0) \cos \gamma + S(t) \sin \beta.$$

The remainder of our discussion will deal with the properties of the solutions of the equations (40), or of equations (35) with (36) and (38) holding.

If $S(t) \equiv 0$, the homogeneous equations have the solutions

$$\begin{aligned} y_1 - y_1^0 &= e^{\lambda t} (A \cos \mu t - B \sin \mu t), \\ y_2 - y_2^0 &= e^{\lambda t} (B \cos \mu t + A \sin \mu t), \end{aligned} \quad (41)$$

as one can readily verify, with A and B constant. In fact, A and B are the values of $y_1 - y_1^0$, and $y_2 - y_2^0$, respectively, at the time $t = 0$. In the general case the solution still has this form, except that the A and B are no longer constant, but are functions of t defined by

$$\begin{aligned} A &= A_0 + \int_0^t e^{-\lambda x} S(x) \cos (\mu x - \beta) dx, \\ B &= B_0 - \int_0^t e^{-\lambda x} S(x) \sin (\mu x - \beta) dx. \end{aligned} \quad (42)$$

In these equations A_0 and B_0 are constant, and are the initial values of $y_1 - y_1^0$ and $y_2 - y_2^0$ respectively.

We are especially interested in the case when S is a constant and $A_0 = B_0 = 0$, i.e. when a constant stimulus is applied to a resting fiber. In this case the quadratures (42) can be effected, and one obtains

$$\begin{aligned} A &= S[\cos(\beta - \gamma) - e^{-\lambda t} \cos(\mu t - \beta + \gamma)], \\ B &= S[\sin(\beta - \gamma) + e^{-\lambda t} \sin(\mu t - \beta + \gamma)]. \end{aligned} \quad (43)$$

Hence, on substituting these values of A and B into (41) we obtain

$$\begin{aligned} y_1 - y_1^0 &= S[e^{\lambda t} \cos(\mu t + \beta - \gamma) - \cos(\beta - \gamma)], \\ y_2 - y_2^0 &= S[e^{\lambda t} \sin(\mu t + \beta - \gamma) - \sin(\beta - \gamma)], \end{aligned} \quad (44)$$

or, somewhat more explicitly,

$$\begin{aligned} y_1 - y_1^0 &= S[e^{t \cos \gamma} \cos(t \sin \gamma + \beta - \gamma) - \cos(\beta - \gamma)], \\ y_2 - y_2^0 &= S[e^{t \cos \gamma} \sin(t \sin \gamma + \beta - \gamma) - \sin(\beta - \gamma)]. \end{aligned} \quad (45)$$

Excitation will occur at the first, third, \dots , roots of

$$y_1 = y_2$$

i.e. of

$$\begin{aligned} e^{\lambda t} [\cos(\mu t + \beta - \gamma) - \sin(\mu t + \beta - \gamma)] \\ = \cos(\beta - \gamma) - \sin(\beta - \gamma) + \frac{y_2^0 - y_1^0}{S}, \end{aligned} \quad (46)$$

and will continue until the second, fourth, \dots , roots respectively. This equation can be simplified slightly, by means of a trigonometric identity, to the form

$$e^{\lambda t} \cos(\mu t + \beta - \gamma + \frac{\pi}{4}) = \cos(\beta - \gamma + \frac{\pi}{4}) + \frac{y_2^0 - y_1^0}{S\sqrt{2}}, \quad (47)$$

and if we set

$$\beta' = \beta + \frac{\pi}{4} \quad (48)$$

we have

$$e^{\lambda t} \cos(\mu t + \beta' - \gamma) = \cos(\beta' - \gamma) + \frac{y_2^0 - y_1^0}{S\sqrt{2}}. \quad (49)$$

For abbreviation set

$$f(t) \equiv e^{\lambda t} \cos(\mu t + \beta' - \gamma), \quad (50)$$

$$\phi(S) \equiv \frac{y_2^0 - y_1^0}{S\sqrt{2}} > 0,$$

and write (49) in the form

$$f(t) = f(0) + \phi(S). \quad (51)$$

The following statement is now immediate:

When the excitation equations (1) have complex roots $\lambda \pm i\mu$ there is a unique admissible substitution (4) reducing these equations to the form (35), with β_1 and β_2 satisfying (38). By a further choice of time unit it is possible to obtain the somewhat simpler form (40). In these equations $\lambda = \cos \gamma < 0$, $\mu = \sin \gamma \neq 0$, and $y_2^0 > y_1^0$, but the parameters are otherwise independent and unrestricted as to sign. Excitation is assumed to occur and persist while $y_1 \geq y_2$.

The general solution of these equations is given by (41) and (42), but in the special case that a constant stimulus S is applied to a resting fiber the quadratures can be effected and the solutions are given by (44). The intensity-time relations are then given by an equation of the form (51) where f and ϕ are defined by (50), excitation lasting while $f(t) - f(0) \geq \phi(S)$. Since $\phi(S) > 0$ for all S , while vanishing asymptotically in S , and since $f(t)$ fluctuates periodically in sign and vanishes asymptotically in t , we have the following possibilities:

If $f(0) > 0$, $f(t)$ can exceed $f(0)$ at most a finite number of times, and if $f(0)$ is an absolute maximum of $f(t)$ for all $t \geq 0$, no excitation is possible for any S . If, however, $f(t)$ exceeds $f(0)$ for some $t > 0$, then for sufficiently large S at least one discharge will be possible, and the rheobase is given by the value of S for which $\phi(S) = f(t_1) - f(0)$, t_1 being the value of t at the first maximum of $f(t)$.

If $f(0) = 0$ the rheobase S_1 is given by $\phi(S_1) = f(t_1)$, and if t_n is the time of the n -th maximum, n discharges are obtainable by making $S \geq S_n$ where $\phi(S_n) = f(t_n)$. The solution S_n exists and is unique for any n .

If $f(0) < 0$, let S_∞ be the unique solution of $\phi(S) + f(0) = 0$, and S_1 the rheobase obtained as in the first case. If $S < S_1$ no excitation occurs; if $S_1 \leq S < S_\infty$ there will be a finite number of discharges; if $S = S_\infty$, there will be infinitely many discharges; and if $S > S_\infty$, then after at most a finite number of discharges a state of permanent excitation will result persisting as long as the constant stimulus S is applied.

This last case of $f(0) < 0$ might seem to be physically impossible,

but if it be supposed that an intensity S_∞ of the stimulus is injurious, then the mechanism breaks down for such stimuli and one still has only a finite number of discharges from any "physiologically admissible" stimulus.

It is to be noted that on this theory the frequency of the discharge under constant stimulation is a fixed characteristic of the nerve fiber, and is independent of the intensity S of stimulation. Only the number of discharges varies with S , and this is potentially infinite for fibers for which $f(0) \leq 0$, but limited in those for which $f(0) > 0$. In order to obtain variation of the frequency with S by a two-factor theory (or, in fact, by an n -factor theory) it is necessary to generalize equations (1) to a form

$$\begin{aligned}\frac{dx_1}{dt} &= f_1(x_1 - x_1^0, x_2 - x_2^0, S), \\ \frac{dx_2}{dt} &= f_2(x_1 - x_1^0, x_2 - x_2^0, S),\end{aligned}\tag{52}$$

where it is supposed that the functions f vanish with their three arguments $x_1 - x_1^0$, $x_2 - x_2^0$ and S . If the functions f are expanded in power series of the three arguments, the linear equations discussed above may be regarded as first-order approximations.

Nevertheless, the linear theory in the periodic case yields, at least qualitatively, not only the possibility of repetitive discharges, but also the depressed state (relative refractoriness) and the ensuing supernormal phase. However for any quantitative checks it will be necessary to study the solutions (41) with A and B constant giving the recovery course after withdrawal of the stimulus, and also the course of development of the two substances with intermittent stimulation.

LITERATURE

- H. A. Blair, 1932. "On the intensity-time relations for stimulation by electric currents," *Jour. Gen. Physiol.*, **15**, 709-729.
 A. V. Hill, 1936. "Excitation and accommodation in nerve", *Proc. Roy. Soc. London*, **119 B**, 305-355.
 A. V. Hill, 1936. "The strength-duration relations for electric excitations of medullated nerve", *Proc. Roy. Soc. London*, **119 B**, 440-453.
 F. Offner, 1937. "Excitation theories of Rashevsky and Hill," *Jour. Gen. Physiol.*, **21**, 89-91.
 N. Rashevsky, 1933. "Outline of a physico-mathematical theory of excitation and inhibition", *Protoplasma*, **20**, 42-56.
 N. Rashevsky, 1938. *Mathematical Biophysics*, The University of Chicago Press.
 G. Young, 1937. "Note on excitation theories", *Psychometrika*, **2**, 103-106.

DIFFUSION IN COLLOIDAL MEDIA

JOHN M. REINER

The University of Chicago

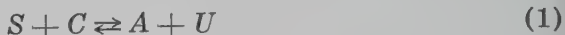
When the molecules of a solute diffuse through a medium containing large colloidal particles, which absorb the diffusing molecules, the latter are transported in the diffusion flow not as free molecules, but as adsorption compounds: solute + colloid. When the colloidal particle is much larger than the molecule of the solute, and has therefore a much smaller mobility, this results in a reduction of the apparent diffusion coefficient for the solute. The biological implications of this are discussed.

In the first approximation the diffusion coefficient of a substance may be determined by considerations of the viscous resistance offered to the moving molecule by the solvent. In this way the well known formula of Einstein for the diffusion coefficient is obtained. (Gyemant 1925). According to it, the diffusion coefficient should be roughly inversely proportioned to the average linear size of the diffusing molecule. Inasmuch as the permeability of the cell membrane is largely determined by the diffusion coefficient (Reiner, 1937) we would expect the permeabilities to depend approximately also on the size of the diffusing molecule. However, it is well known that different molecules, having approximately the same size, permeate the cell sometimes at very different rates.

The present paper discusses the possibility that the diffusion process may be influenced by the adsorption of the diffusing molecule by larger colloidal particles. If the diffusing molecule is transported in form of such an adsorption compound, then its diffusion coefficient will be considerably lowered, when the carrying colloidal particle is very large. Of two molecules of same size, but different chemical nature, one may be strongly adsorbed, the other not. Thus we may find large differences in the diffusion coefficient and in permeability.

The effective diffusion coefficient in a colloidal solvent may be determined upon the assumption that the solute and the colloid establish an adsorption equilibrium, while both experience the usual resistance to motion from the solvent medium (e.g., water). The adsorption is calculated by means of the law of mass action. This amounts to assuming that the adsorption is stoichiometric. In the simple case, a mole-

cule of the solute (S) is adsorbed upon an active group of the colloid molecule (C) to form one molecule of adsorption compound (A), thus:



U is the heat of formation of a molecule of A . Let the concentrations of free S , C , A be n_s , n_c , n_a molecules cm^{-3} ; then the total concentrations of solute and colloid respectively are:

$$N_s = n_s + n_a; \quad N_c = n_c + n_a. \quad (2)$$

The total diffusion current, J , of S (no. molecules of solute crossing per sec. an area of 1 cm^2 normal to the flow) is the sum of the currents J_a and J_s of bound (A) and free (S) particles. For, if the distribution of N_s is non-uniform, the same will in general be true of n_s and n_a , even though N_c is constant (as will be assumed in the following). Thus there will be a gradient of n_a even when there is no gradient of total colloid N_c . Moreover, by Fick's law,

$$J_s = -D_s \text{grad } n_s; \quad J_a = -D_a \text{grad } n_a,$$

where D_s and D_a are the diffusion coefficients of the substances S and A . Hence:

$$J = J_s + J_a = -D \text{grad } N_s,$$

where, by Eq. (2) and the constancy of N_c :

$$D = D_s[1 - (\partial n_a / \partial N_s)] + D_a(\partial n_a / \partial N_s) \quad (3)$$

is the effective diffusion coefficient of the solute* S . From Eq. (3) it appears that D is the average of D_s and D_a , with a weighting factor $\partial n_a / \partial N_s$. It will be shown below that $0 \leq \partial n_a / \partial N_s \leq 1$ for all N_s and N_c .

For Eq. (1), the law of mass action takes the form:

$$N_0 n_a = n_s n_c, \quad (4)$$

where N_0 is the reciprocal of the equilibrium constant, and has the dimensions of a concentration. It may be interpreted as the N_c value for which $n_a = n_s$, i.e., for which half the solute is adsorbed. It is given by the Arrhenius equation:

$$\log N_0 = \log Z_0 - U/kT, \quad (5)$$

where k is the Boltzmann constant, T is the absolute temperature, and

* If the diffusion coefficients of substances C and A are not equal, N_c will not remain constant as assumed above. As C is a colloid, it will have very large molecules compared to those of S ; it is thus reasonable to suppose that, to a first approximation, $D_a = D_c$. If this is not the case, the above analysis will require generalization.

Z_0 a constant. Expressing n_s and n_c in terms of N_s , N_c , and n_a by means of Eq. (2), one finally obtains the equation for n_a as an implicit function of N_s and N_c :

$$N_0 n_a = (N_s - n_a)(N_c - n_a). \quad (6)$$

To solve this, it is convenient to introduce the dimensionless quantities:

$$x = N_s/N_c; \quad y = n_a/N_c; \quad z = N_0/N_c. \quad (7)$$

It then takes the form:

$$zy = (x - y)(1 - y), \quad (8)$$

and has the solution:

$$y = \frac{1}{2}[x + 1 + z - \sqrt{(x + 1 + z)^2 - 4x}]. \quad (9)$$

The other solution, corresponding to the positive sign of the radical, is excluded on physical grounds: it makes y everywhere larger than x for $z \geq 0$, while, from Eqs. (2) and (7), x must always exceed y , and $z \geq 0$. Eq. (9) represents a one-parameter family of curves in the x - y plane (see Fig. 1). Regardless of the value of z , the amount of S adsorbed per molecule of C , y is zero for $x = 0$, and rises monotonically to $y = 1$ for $x = \infty$.

The parameter z is proportional to N_0 , which in turn varies exponentially with the heat of formation of A . The interpretation of

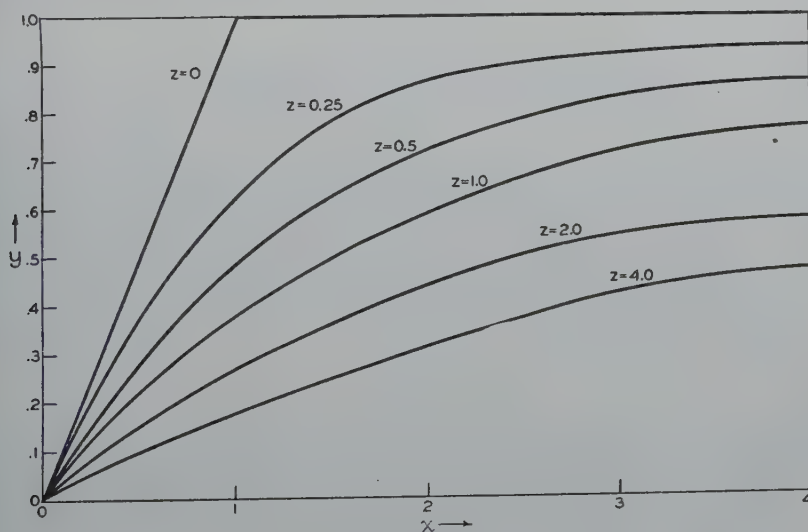


FIGURE 1

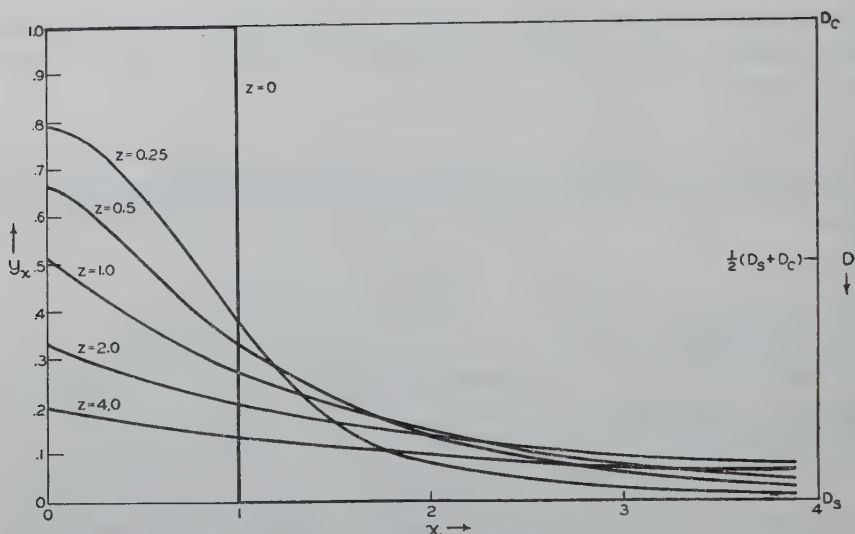


FIGURE 2

Fig. 1 thus follows readily. As U approaches ∞ (adsorption extremely exothermic), z approaches zero, so that y tends to a line consisting of the straight line $y = x$ for $0 \leq x \leq 1$, and the straight line parallel to the x -axis, $y = 1$, for $x \geq 1$. That is to say: if the reaction is pronouncedly exothermic, and C is in excess of S , ($x \leq 1$), all of S will be adsorbed; in the presence of an excess of S , ($x \geq 1$), an amount of S exactly equal to that of the C present will be adsorbed. For finite U , ($z > 0$) the amount of adsorption is less than this limit, so that there is always some free solute for every $x < \infty$.

The first derivative, $y_x = \partial n_a / \partial N_s$, is given by:

$$y_x = \frac{1}{2} \{ 1 - (x - 1 + z) / [(x + 1 + z)^2 - 4x]^{\frac{1}{2}} \}. \quad (10)$$

This family of curves is represented in Fig. 2. The function falls monotonically from $1/(z + 1)$ at the origin to the asymptotic value zero for $x = \infty$. On the other hand, it does not always vary monotonically with z , as shown in Fig. 3. If one differentiates Eq. (10) with respect to z , and sets the result equal to zero, y_x is found to possess a maximum with respect to z . The value of z at this maximum is connected with x by the simple relation:

$$x = 1 + z. \quad (11)$$

Thus, since $z \geq 0$, the maximum can exist only for $x > 1$. For $x \leq 1$, the variation of y_x with z is monotonic. Eq. (11) can also be written:

$$N_0 = N_s - N_c. \quad (11')$$

Thus N_0 is the excess of solute S over colloid C at the z -maximum. The

maximum is accordingly attained for smaller excess of solute, the more exothermic the reaction.

The previous assertion that $0 \leq \partial n_a / \partial N_s \leq 1$ can now be justified from Eq. (10). For the criterion that the second term of y_x shall be no larger in absolute value than unity is found to be simply $z \geq 0$, which we know to be always true. Consequently, the entire expression in braces cannot become either negative or larger than 2, from which

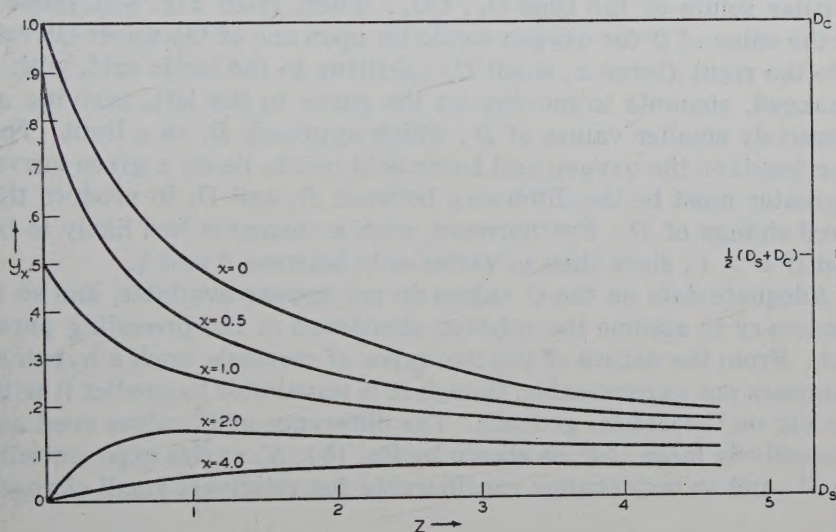


FIGURE 3

follows the statement to be proved. Thus the expression (3) for D is seen to be a true average of D_s and D_a , lying between them in magnitude. The variation of D may thus be simply obtained from that of y_x by altering the scale; for D is a linear function of y_x , and $D = D_s$ when $y_x = 0$, $D = D_c$ when $y_x = 1$. Accordingly, the scale on the right-hand side in Figs. 2 and 3 gives D . If $D_a < D_s$ (which is virtually always the case), D increases whenever y_x decreases and conversely. D thus in this case has a minimum wherever y_x (vide supra) has a maximum.

The variation of D with z suggests a possibility of accounting for the conclusions of Landahl (Landahl, 1939) on the diffusion coefficient in unfertilized *Arbacia* eggs. From available data, he calculates that D for oxygen may be as much as 10^3 times as large as D for lactic acid. Since D is the mean of D_a and D_s , these would have to differ by the same factor of 10^3 if the change in D is to be accounted for entirely by the change in y_x , since the latter lies always between 0 and

1. This is not too improbable an assumption, for the values of colloidal coefficients of self-diffusion may fall extremely low, depending upon the density and structure of the particular colloid.

Let us suppose that we are comparing the two solutes at the same concentration, and that the density of the colloid has not varied, so that x is the same for both cases. Suppose, as is reasonable, $x < 1$. Then the further assumption necessary is that the value of U is quite large for such a solute as lactic acid, and very low for a non-ionic and non-polar solute of the type O_2 , CO_2 . Then, from Fig. 3 it follows that the value of D for oxygen would lie upon one of the upper curves, far to the right (large z , small U); shifting to the lactic acid, with x unchanged, amounts to moving up the curve to the left, arriving at successively smaller values of D , which approach D_a as a limit. The closer together the oxygen and lactic acid points lie on a given curve, the greater must be the difference between D_a and D_s to produce the desired change of D . Furthermore, such a change is less likely to be found if $x > 1$, since then y_x varies only between 0 and $\frac{1}{2}$.

Adequate data on the U values do not appear available, and so it is necessary to assume the relation mentioned in the preceding paragraph. From the nature of the two types of molecule, such a hypothesis appears not unreasonable, though it is impossible to predict it with certainty on theoretical grounds. The difference of U values need not be excessively large; for, as shown by Eq. (5), N_0 varies exponentially with U , and so may change considerably for relatively small changes of U .

It is also possible to consider keeping the solute fixed and changing the colloid. For $x < 1$, D will decrease if the colloid is replaced by one of a more active type (larger U for a given solute). For $x > 1$, the same will hold up to a certain degree of colloid reactivity, after which a more active colloidal medium will cause an increase in the value of D .

In a similar fashion, the variation of D with x may be obtained from the right-hand scale of Fig. 2. From this, D is observed to increase with increasing solute concentration, the increment for a given added amount of solute being sharpest in the neighborhood of $x = 1$. A caution is necessary, however, if this graph is to be applied for high values of x . For the principal assumption underlying the mass action law in the simple form of Eq. (4) is that the solution shall be dilute with respect to all constituents. Since x is a relative concentration by Eq. (7), it follows that the formulas are applicable for very high values of x only if N_0 is so low that, for the x under consideration, N_s still satisfies this restriction.

The author wishes to acknowledge the helpful advice and assist-

ance of Professor Carl Eckart, of the Department of Physics.

This investigation has been made possible by a grant from the Rockefeller Foundation to the University of Chicago.

LITERATURE

Gyemant, A. 1925. *Grundzüge der Kolloidphysik*. F. Vieweg, Braunschweig.

Landahl, H. D. 1939. "Mathematical Biophysics of Cell Respiration, II." *Bull. Math. Biophysics*, 1, 1-17.

Reiner, John M. 1937. "Diffusion and Biological Membrane Permeability." *Growth*, 1, 313-327.

